Molecular basis of muscle contraction

By the end of this lecture the student will be able to:

1. Describe skeletal muscle structure–function relationships.
2. Summarize the excitation-contraction coupling.
3. Recognize the mechanism of cross bridge cycle
4. Interpret the role of cytosolic calcium in muscle contraction and relaxation.

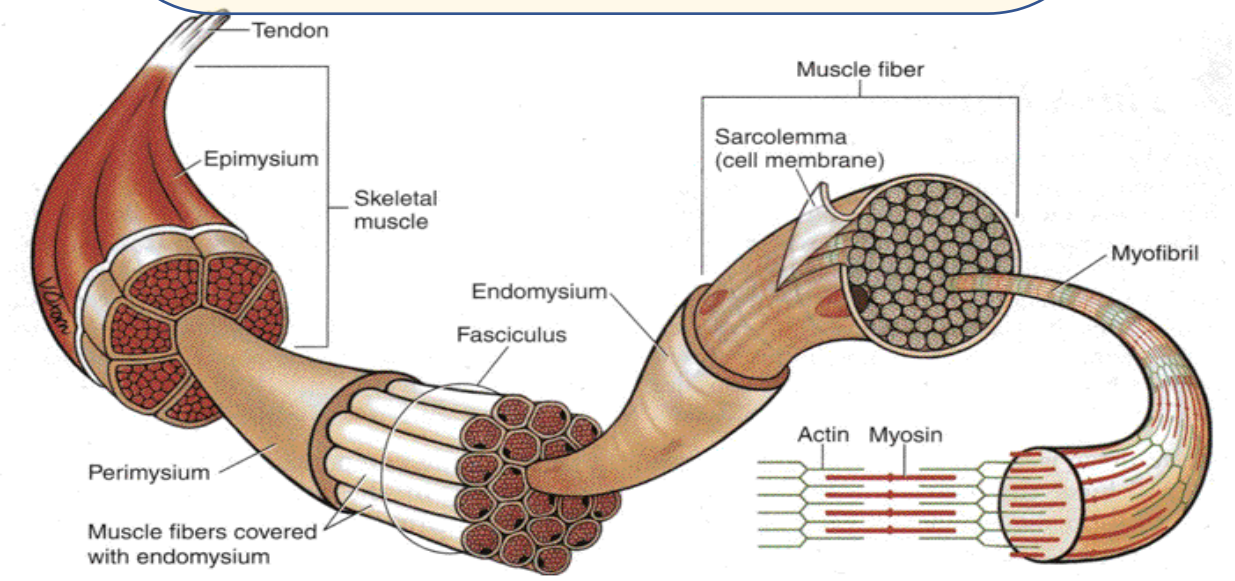

Figure (1): Skeletal muscle structure

I-Skeletal muscle structure and function relationship:

1- Skeletal muscle is made up of individual muscle fibers that are the "building blocks" of the muscular system.
2- Muscle fibers are arranged in parallel between the tendinous ends, so that the force of contraction of the units is additive.
3- Muscle fiber cells are electrically insulated by the endomysium with no syncytialbridges between cells.
4- Muscle fiber sarcoplasm contain myofilaments
5- There are two myofilaments types: thick myosin and thin actin
6- Myofilaments are arranged to form the **sarcomere** which is the **functional contractile unit** of the muscle fiber

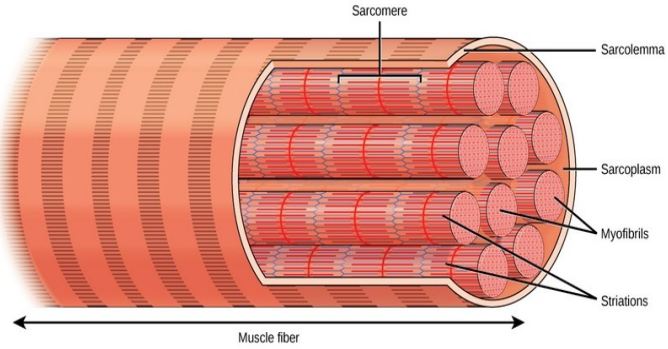

Figure (2): Skeletal muscle striations

7- The sarcomere structure:

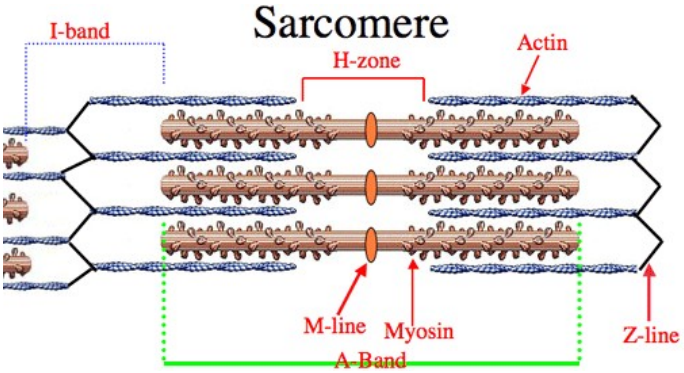

Figure (3): Skeletal muscle sarcomere

- **Dark A band:**
- Formed of thick myosin myofilament
- **Light I band:**
- Formed of thin actin myofilaments not covered by myosin
- **Z lines:**
- Connect thin filaments
- Sarcomere is the distance between 2 Z lines

Muscle contract by sliding filament theory:

- The contraction of the muscle cell occurs as the thin filaments slide past the thick filaments.

- **Z lines Come closer during contraction, sarcomere shortens**
- Thick and thin filaments size do not change
- **Dark A band: Not shortened during contraction**
- **Light I band: smaller during contraction**

8-Muscle myofilaments:

A-Thick myosin:

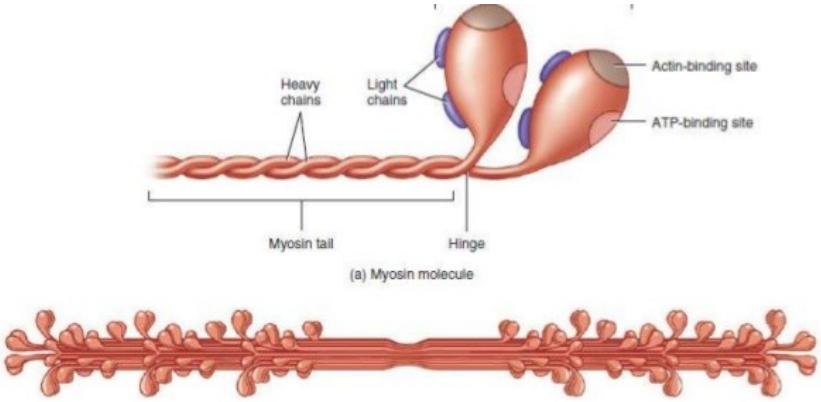

Figure (4): Thick myosin filament

- **Tail:** 2 heavy polypeptide chains coiled forming a double helix
- **Arm:** extended part of the tail, form with the head (**cross bridges**) that can move back and forth
- **2 Hinge portions of the tail:**
  - First: It allows the vertical movement, so that the cross bridge can bind to actin.
  - Second: It allows the head flexion and provides power stroke for muscle contraction
- **Myosin head contains 2 binding sites:**

- **ATP binding site:** This site has ATPase activity. When ATP molecule binds, it is hydrolyzed into ADP, Pi + energy. The energy is transferred to myosin head (i.e. energizing myosin head).

- **Actin binding site:** This site has a strong attraction for binding to actin.

B-Thin actin filaments

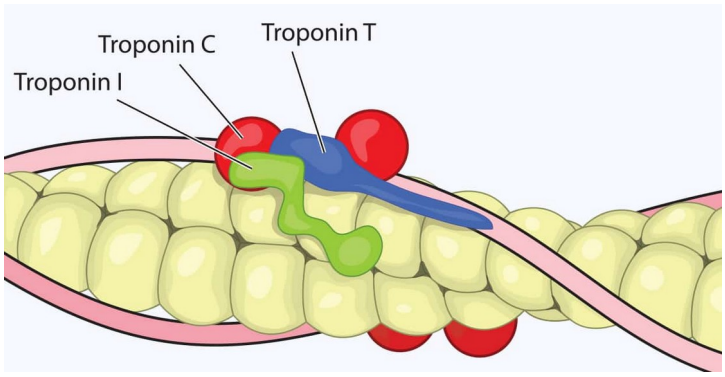

Figure (5): Thin actin filaments

- **1-Actin double helix:**

- Double helix with specific myosin binding site (active site) for the attachment of the myosin cross bridges.

- **2-Tropomyosin:**

- Relaxing protein that blocks the interaction between actin and myosin cross bridges by covering the myosin binding sites

- **3- Troponin protein complex:**

  - **Troponin T:**

Fix tropomyosin to cover active sites during muscle relaxation

  - **Troponin C:**

Bind calcium to initiate contraction

  - **Troponin I:**

Bind to actin

II-Excitation contraction coupling

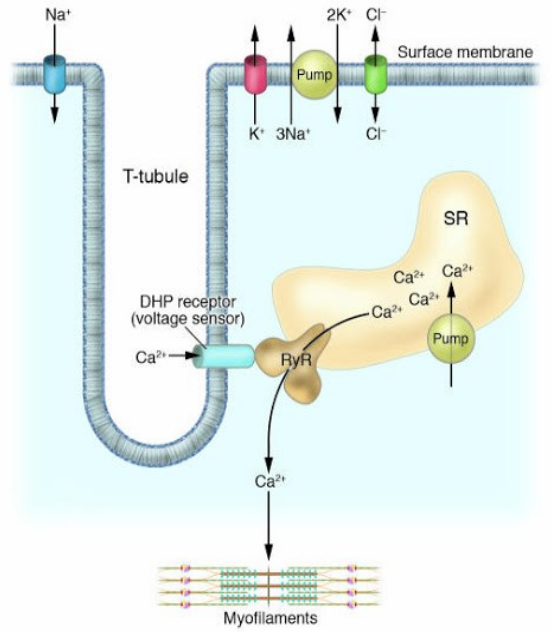

Figure (6): Excitation contraction coupling

- It is the process by which depolarization of the muscle fiber initiates muscle contraction.

1. Depolarization wave spread inward along T tubules evokes conformational changes in **dihydropyridine receptors (DHP) the voltage sensor**, activating it.
2. Through the mechanical coupling (connection) between DHP receptors and ryanodine receptors, a conformational change in **ryanodine receptors (the Ca++ release channels in the SR)** occurs, causing it to open.
3. The sarcoplasmic reticulum (SR) has a **high concentration of Ca2+**. Thus, there is a strong electrochemical gradient for Ca2+ to diffuse from the SR into the cytosol.
4. This allows Ca^{+2} out poring from the terminal cisterns of the SR into the cytoplasm of the muscle fiber.
5. Increase sarcoplasmic calcium
6. Binding of **calcium to troponin C**, induce conformational change in troponin-tropomyosin complex.
7. Tropomyosin moves laterally **exposing "uncovering" the myosin binding sites** on the actin
8. Cross linkages between myosin and actin, the start of cross bridge cycle

Cross bridge cycle.

III- Cross bridge cycle

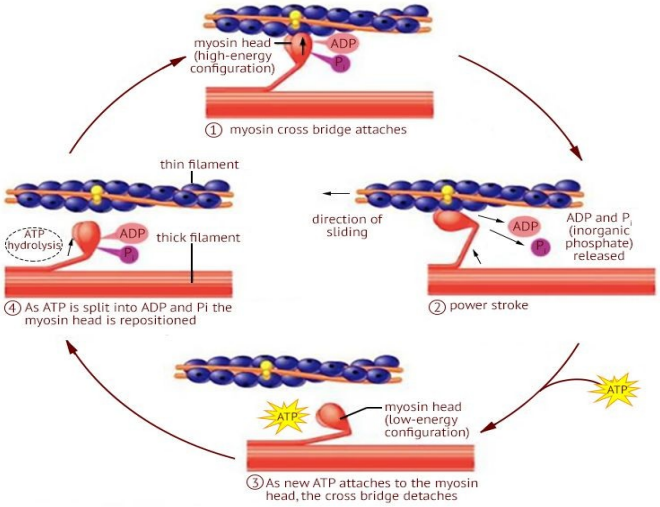

Figure (7): cross bridge cycle

The steps of cross bridge cycle (Sliding filament theory): walk along theory

1-Binding:

Energized myosin cross-bridge **has affinity for actin** and bind to the **exposed** binding site on actin

2-Bending (power stroke):

- The cross bridge flexes (bends), pulling the thin filament inward towards the center of the sarcomere
- At the same time, ADP and Pi. are released
- Chemical energy is transformed to mechanical energy

3-Detachment:

- A new ATP molecule bind to its site on myosin cross bridge
- Disconnection of the cross-bridge from actin

4-Repositioning:

- Re-energizing of myosin cross bridge: Hydrolysis of ATP molecule gives rise to ADP, Pi & energy.
- Energy is transferred to the which myosin cross bridge returns to its high-energy conformation
- Myosin returns to its normal perpendicular position (Cocked position) to bind to a new active site.

- During contraction, there are multiple cross bridge cycles
- The greater the numbers of cross bridges in contact with the actin filament, the greater is the force of contraction.
- Each one of the cross bridges is operating independently of all others
- But, the multiple cross bridge cycling is coordinated sequentially to prevent all cross bridges from either being connected or disconnected at the same time.

IV-Role of calcium in muscle contraction:

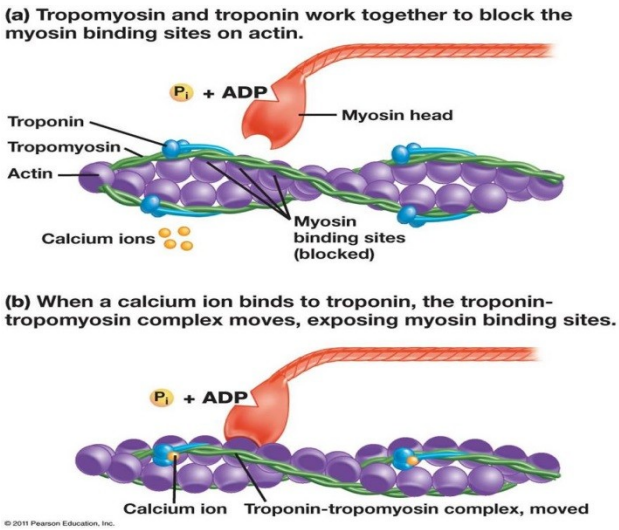

Figure (8):Troponin-tropomyosin complex

- As long as Ca++ ions are available
- The cross bridge cycles are repeated
- Muscle contraction continues

V- Muscle relaxation mechanism:

- It is an active process.
- It depends on active reuptake of Ca++ into the SR by Ca++ pump.
- Return (reduction) of intra-sarcoplasmic Ca++ concentration to the resting level
- Release of Ca++ ions from troponin C.

- Tropomyosin moves back to cover the active sites on actin.
- Cessation of the interaction between actin and myosin.

Rigor mortis

After death, due to ATP depletion, the body becomes stiff and muscle will remain rigor until the cellular proteins begin to breakdown usually within 24 – 48 hours.

Muscle contracture:

It is a prolonged muscle contraction without relaxation, in absence of stimulation. It is caused by sustained elevation of cytoplasmic Ca++ by an excessive release or by decrease in the reuptake by the sarcoplasmic reticulum.